e9 61. (Amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a proximal 445 bp of the murine WAP promoter which includes a transcription initiation site.

82. (Amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a proximal 445 bp of the murine WAP promoter which includes e10 a transcription initiation site and wherein the WAP promoter directs expression of the heterologous gene in a human mammary carcinoma cell when the vector is introduced into the cell.

87. (Amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a proximal 445 bp of the murine WAP promoter e11 which includes a transcription initiation site.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - iii).

REMARKS

Rejection of Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 38, 44, 55, 59, 74-81, 91 and 92 under 35 U.S.C. §112, second paragraph

Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 38, 44, 55, 59, 74-81, 91 and 92 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 2).

The Examiner states that it is "unclear what is intended to be claimed: a retroviral vector, a MMTV provirus or a plasmid" (Office Action, page 3). The Examiner further states that "[i]t is unclear as to the metes and bounds of what would be considered 'U3 sequence homologous to a PCR amplification product" is "vague and renders the claims indefinite' (Office Action, page 3).

The claims relate to a retroviral vector. In order to more clearly define the invention, the claims have been amended to recite the following:

> A retroviral vector comprising a heterologous gene placed under transcriptional control of a MMTV U3 sequence,
>
> wherein the MMTV U3 sequence is obtainable using a PCR amplification product that is amplified using primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a PCR template comprising a MMTV provirus,
>
> and wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell.

The Examiner states that "the term 'proximal 445 bp of the murine WAP promoter' . . . is vague and renders the claims indefinite" (Office Action, page 3). The Examiner states that "[m]urine WAP promoter encompasses promoter sequences derived from various murine species" and that "[i]t is unclear what proximal 445 bp of which WAP promoter is intended" (Office Action, page 3).

Applicants respectfully disagree. As noted in the MPEP:

> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph > by providing clear warning to others as to what constitutes infringement of the patent (MPEP, 8th ed., revised Feb. 2003, Section2173.02, page 2100-199).

As pointed out in the previously filed Amendment mailed to the U.S. Patent Office on September 5, 2002, Applicants clearly teach in the specification as filed that "***the region of the WAP promoter which is required for mediating the mammary gland specificity is a 320 bp XhoI\XbaI restriction fragment (-413 to -93)***" and cite a specific reference in support thereof *i.e.,* Kolb, A.F. *et al., Biochem. Biophys. Res. Comm., 217:*1045-1052 (1995); Reference AR in the Information Disclosure Statement mailed to the U.S. Patent Office on March 16, 1999

(specification, page 11, lines 17-19). Figure 1 of Kolb *et al.* clearly shows the "[s]tructure of ***the proximal region of the WAP promoter***", and "[i]mportant restriction sites" such as a "320bp XhoI/XbaI restriction fragment (-413 to -93)" (Kolb *et al.*, Figure 1 legend). Knowing the ***region of the WAP promoter which is required for mediating the mammary gland specificity*** and having the ***structure of the proximal region of the WAP promoter*** , one of skill in the art is clearly apprised of a "proximal 445 bp of the murine WAP promoter" for use in expressing a heterologous gene operably linked thereto in a human mammary cell. Thus, the phrase "proximal 445 bp of the murine WAP promoter" is definite.

The Examiner states that the phrase "select from the group Herpes Simplex Virus thymidine kinase gene . . .**or** cytokine genes" in Claims 11, 32 and 59 is vague and renders the claims indefinite and suggests replacing "or" with "and" (Office Action, pages 3-4).

The claims have been amended in accordance with the Examiner's suggestion.

Rejection of Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36-45 and 47-94 under 35 U.S.C. §112, first paragraph

Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36-45 and 47-94 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner states that the "expression of a β-galactosidase in explanted normal primary human mammary tissue infected with vectors pMMTV-BAG and pWAP-BAG is not considered to enable therapeutic gene expression under the control of a MMTV promoter or a WAP promoter, since expression of a marker gene does not correlate with expression of a gene *in vivo*, such that the expression provides therapeutic effect for a therapy" (Office Action, page 6). The Examiner further states that the "specification fails to provide adequate guidance and evidence for the sufficient expression of any heterologous gene or any therapeutic gene under the control of any MMTV promoter or any WAP promoter in the retroviral vector or other vector for sufficient time *in vivo* such that therapeutic effects are provided for a particular disease or disorder, or for using said retroviral vector expressing any heterologous gene or therapeutic gene for the treatment of disorders or diseases of human mammary cells *in vitro* or *in vivo*" (Office Action, page 7). The Examiner cites Verma *et al.*, Eck *et al.*, Gorecki *et al.* and Aebischer *et al.* in support of the rejection.

Applicants respectfully disagree. As pointed out in the previously filed Amendments, in the specification as filed, Applicants show how to make a retroviral construct in which β-gal is placed under the transcriptional control of a WAP or a MMTV regulatory region (Examples 1-3); how to make retroviral particles produced by culturing a packaging cell line harboring the retroviral vector and one or more constructs coding for proteins required for the retroviral vector to be packaged (Example 4); and how to infect mammary cells using supernatant containing the retroviral particles *in vitro* (Example 4). Applicants also show methods for assessing whether the WAP or MMTV-U3 regulatory sequence drives expression of a heterologous gene within a vector in human cells, such as primary human mammary gland cells (specification, pages 30-31). Applicants further describe how to make a retroviral vector carrying the cytochrome P450 gene, a therapeutic gene which encodes a protein that catalyses the hydroxylation of the commonly used cancer prodrugs CPA and ifosfamide to their active toxic forms, under control of the WAP regulatory sequence; how to encapsulate a packaging cell line containing the claimed construct and how to implant the capsules which produce viral particles in or around mammary tissue to ensure continuous release of virus *in vivo* (Example 5).

As also pointed out previously, it is well known in the art that the structure and life cycle are highly conserved among retroviruses. The sequence of numerous therapeutic genes, in addition to the examples of therapeutic genes Applicants provide in the specification (*e.g.*, page 7, line 22 - page 8, line 2), are also well known in the art. One of skill in the art can obtain a known gene and insert the gene (*i.e.*, a heterologous gene such as a therapeutic gene) into a retroviral vector using well known techniques (*e.g.*, techniques using restriction enzymes or PCR technology). To obtain or isolate a gene using commercial sources, restriction enzymes or PCR technologies followed by ligation of the gene with a retroviral vector backbone are routine methods to those of skill in the art (*e.g.*, see Sambrook *et al., Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, 1989).

It is also well known in the art that retroviral vectors function according to one main principle, *i.e.*, they exploit the cellular machinery for their own propagation. Accordingly, Applicants demonstration that a MLV retroviral vector comprising a WAP or MMTV regulatory region can generate a retroviral particle which infects living cells, that the retroviral vector can integrate the incorporated heterologous gene into the genome of the target cell and can induce

expression of the introduced heterologous gene in primary human mammary cells, including human mammary carcinoma cells, provides sufficient enablement of Applicants' claimed invention. Finally, as pointed out in the previously filed Amendments, the general feasability of the *in vivo* use of retroviral vectors to treat a disease is well accepted in the art and it is universally accepted by those of skill in the art.

Although the *in vivo* experiments are time consuming, it does not follow that such experiments are undue for the skilled practitioner. The court has clearly stated that:

> Enablement is not precluded by the necessity for experimentation such as routine screening... However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'... The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having due regard for nature of the invention and the state of the art... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (In re Wands, 1400 U.S.P.Q.2d 1400, 1404 (CAFC 1988)).

In Wands, the court held:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics In re Wands, 1400 U.S.P.Q.2d 1400, 1406 (CAFC 1988)).

Thus, a considerable amount of experimentation is permissible if, as here, it is routine. *Clearly, the court recognized that practitioners of the art could not **predict** which hybridomas would be negative, and that **screening** of hybridomas to determine which hybridomas were negative and which hybridomas were positive, which entails time consuming in vivo experiments (e.g., immunizing animals with myeloma cells to make hybridomas), is **routine** to those of skill in the art.* Furthermore, Applicants have provided a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Given the state of the art, the guidance in

the specification, and detailed examples regarding the claimed epitopes, it would not require undue experimentation to make and use the invention as claimed.

Thus, undue experimentation is not required to practice Applicants' claimed invention. That is, using the guidance provided by Applicants in the specification as filed and the knowledge in the art, a person of skill in the art is fully enabled to handle, propogate and modify retroviruses other than the MLV vector Applicants used to exemplify the invention, in order to obtain retroviral vectors comprising a heterologous gene placed under transcriptional control of a MMTV or WAP regulatory region. Furthermore, using routine experimentation and the guidance Applicants provide in the specification, one of skill in the art can use Applicants' claimed vectors to express the heterologous gene *in vitro, ex vivo* or *in vivo* in human cells, for example, to treat human mammary carcinoma.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 53, 54, 58-61, 67-69, 82, 83 and 85-88 under 35 U.S.C. §102(e)

Claims 53, 54, 58-61, 67-69, 82, 83 and 85-88 are rejected under 35 U.S.C. §102(e) "as being anticipated" by Barber *et al.* (Office Action, page 14). The Examiner states that Barber *et al.* teach "preparation of a recombinant retroviral vector or retrovirus expressing a cytotxic gene, such as a cytosine deaminase gene, under control of WAP promoter, production of vector particle by using producer cells, and a pharmaceutical composition comprising said retroviral vector, and retroviral particles and a pharmaceutical acceptable carrier or diluent" (Office Action, page 15).

Applicants respectfully disagree. Nevertheless, in order to expedite prosecution of the referenced application, the claims have been amended, and as amended, are directed to a retroviral vector comprising a heterologous gene placed under transcriptional control of *a proximal 445 bp of the murine WAP promoter which includes a transcription initiation site*, wherein the WAP promoter directs expression of the heterologous gene in a cell when the vector is introduced into the cell. Applicants do not waive their rights to pursue the subject matter of original Claims 53, 54, 58-61, 67-69, 82, 83 and 85-88 in a continuing application.

Barber *et al.* do not teach a retroviral vector comprising a heterologous gene placed under transcriptional control of *a proximal 445 bp of the murine WAP promoter which includes a transcription initiation site.*

Therefore, Barber *et al.* do not anticipate Applicants' claimed invention, particularly as amended.

Rejection of Claims 53, 54, 58-61, 67-69, 82, 83, 85-88 and 90 under 35 U.S.C. §103(a)

Claims 53, 54, 58-61, 67-69, 82, 83, 85-88 and 90 are rejected under 35 U.S.C. §103(a) "as being unpatentable over" Dranoff *et al.* in view of Mehigh *et al.* and Shao *et al.* (Office Action, pages 15-16). The Examiner states that Dranoff *et al.* teach subcloning DNA sequence encoding cytokine . . . and adhesion molecules into retroviral vector MFG which contains Moloney murine leukemia virus (Mo-MuLV) long terminal repeat (LTR) and the resulting construct are introduced into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells" (Office Action, page 16). The Examiner further states that Dranoff *et al.* teach that "transduced B16 cells are inoculated subcutaneously into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene" (Office Action, page 16). The Examiner states that Mehigh *et al.* teach development of a recombinant BLV vector for delivery of a bGRF gene into bovine cell, "wherein the bGRF gene is under the control of WAP promoter of MMTV promoter" and "preparation of virus particles and the use of said viral particles to deliver the bGRF gene by viral infection into fresh MDBK cells" (Office Action, page 17). The Examiner cites Shao *et al.* as teaching "microcapsules composed of collagen and encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene into said microcapsules" wherein the secretion of GM-CSF in the culture medium was monitored (Office Action, page 17). It is the Examiner's opinion that:

> It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the Mo-MuLV LTR as taught by Dranoff with WAP promoter as taught by Mehigh for the construction of a recombinant retroviral vector containing any desired gene, a recombinant retrovirus containing said retroviral vector, or packaging cells harboring said retroviral vector, and a capsule encapsulating said packaging cells for the expression of any desired gene product in a cell, because Mo-MuLV LTR and WAP promoter both are regulatory sequences derived from LTR and they both have function of directing gene

> expression, and Dranoff and Mehigh teach construction of viral vector expressing a desired gene under the control of either WAP promoter or Mo-MuLV LTR . . . One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce a retroviral vector comprising a heterologous gene or a therapeutic gene under the control of a WAP regulatory sequence, a recombinant retroviral particle produced by culturing a packaging cell line harboring said retroviral vector, a retroviral provirus carrying a construct comprising a heterologous gene or a therapeutic gene under the control of a WAP regulatory sequence as taught by Dranoff and Mehigh, and a capsule encapsulating the packaging cells for monitoring the secretion of gene product in cell culture medium as taught by Shao with reasonable expectation of success (Office Action, pages 17-18).

Applicants respectfully disagree. Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.*

There is no particular teaching in the art cited directing the skilled person to produce a retroviral vector comprising a heterologous gene placed under control of a WAP regulatory sequence which directs expression of a heterologous gene in a cell when the vector is introduced into the cell.

Dranoff *et al.* "generated a variety of recombinant retroviruses encoding different potential immunomodulators and compared the vaccination properties of both live and irradiated tumor cells transduced by the viruses in several different tumor models" (Dranoff *et al.*, page 3539, column 2). Dranoff *et al.* used the an MFG retroviral vector system in which the Mo-MuLV LTR was used to express 10 molecules in the model (Dranoff *et al.*, Figure 1). Based on their results, Dranoff *et al.* state that an important implication of their system is "the combination of ***high titer and high gene expression afforded by the MFG vector system***" which would "obviate the need for selection of transduced cells among a bulk tumor cell population thereby minimizing the time required for culturing primary tumor cells prior to vaccination and maximizing the antigenic heterogeneity represented in the vaccinating inoculum" (Dranoff *et al.*, page 3543, column 1, emphasis added). As noted by the Examiner, Dranoff *et al.* do not teach "using WAP promoter

for the expression of a gene in a retroviral vector, and a capsule encapsulating the packaging cell line, said capsule comprising a porous capsule wall surrounding said packaging cell line" (Office Action, page 16).

Mehigh *et al.* constructed plasmids in which the gene encoding synthetic bovine growth hormone-releasing factor (bGRF) was fused to the WAP or the MMTV promoter. Mehigh *et al.* teach that "[t]hese plasmids were able to induce transcription of bGRF upon transfection into . . . bovine kidney cells [MDBK cells] and induction with a lactogenic hormonal milieu . . . or dexamethasone" (Mehigh *et al.*, abstract). Mehigh *et al.* further teach that when the "constructs were cloned into a BLV vector in place of its oncogenic region, and transfected into MDBK cells, bGRF was expressed" and that "[v]iral particles were prepared from these cultures and used to deliver the bGRF gene by viral infection into fresh MDBK cells (Mehigh *et al.*, abstract). Mehigh *et al.* also teach that "***[v]irus infection produced a much lower level of RNA expression, and no detectable protein expression***" (Mehigh *et al.*, page 691, column 2, emphasis added).

Shao *et al.* studied whether prolonged delivery of GM-CSF can be achieved by encapsulating GM-CSF-secreting cells in semi-permeable macrocapsules (Shao *et al.*, page 59, column 1). Based on their results, Shao *et al.* teach that their study "demonstrates the merit of this cell encapsulation system" and "suggests an alternative mode of cytokine delivery and provides basis for other cell-based artificial organ designs" (Shao *et al.*, page 60, column 1). Shao *et al.* do not discuss use of WAP regulatory sequences.

The teachings in the cited art provide no motivation to substitute the Mehigh *et al.* WAP promoter system with the Dranoff *et al.* MFG system to produce "a retroviral vector comprising a heterologous gene or a therapeutic gene under the control of a WAP regulatory sequence" (Office Action, page 18), because the Dranoff *et al.* MFG vector system affords ***"high titer and high gene expression"***. There is no indication in the cited art that the Mehigh *et al.* WAP promoter system would produce the high titer and gene expression of the MFG system. Moreover, one of skill in the art would clearly not be motivated to substitute the Dranoff *et al.* MFG vector system, which affords ***"high titer and high gene expression"***, with the Mehigh *et al.* WAP promoter system, which generates viral particles that resulted in ***"no detectable protein expression"***, to produce "a recombinant retroviral particle produced by culturing a packaging cell line harboring said retroviral vector, a retroviral provirus carrying a construct comprising a heterologous gene or

a therapeutic gene under the control of a WAP regulatory sequence and a capsule encapsulating the packaging cells ***for monitoring the secretion of gene product*** in cell culture" (Office Action, page 18). Shao *et al.* do not provide the teaching that is lacking in the Dranoff *et al.* and Mehigh *et al.* references.

In discussing obviousness, the court has stated that:

> [a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . The critical inquiry is whether 'there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention' (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*13 USPQ2d 1737 at 1765).

There is nothing in the prior art as a whole to *suggest* the desirability, and thus obviousness of making Applicants' claimed invention. The prior art combination of record has been made with the advantage of impermissible hindsight, and thus, the rejection is legally improper. That is, the Examiner has ***not*** taken into account "***only*** knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made" and has included "knowledge gleaned ***only*** from applicant's disclosure" (*In re McLaughlin*, 170 U.S.P.Q. 209, 212, (CCPA 1971), emphasis added). In making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of the desirability of producing a retroviral vector comprising a heterologous gene placed under control of a WAP regulatory sequence which directs expression of a heterologous gene in a cell when the vector is introduced into the cell. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicants' disclosure for the suggestion that the cited references should be combined and the expectation of success (*In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531-1532 (Fed. Cir. 1988)). In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Dranoff *et al.* in view of Mehigh *et al.* and Shao *et al.* do not render obvious Applicants' claimed invention. Furthermore, in order to expedite prosecution of the referenced application, the claims have been amended, and as amended, are directed to a retroviral vector comprising a heterologous gene placed under transcriptional control of *a*

proximal 445 bp of the murine WAP promoter which includes a transcription initiation site. The combined teachings of Dranoff *et al.* in view of Mehigh *et al.* and Shao *et al.* also do not render obvious Applicants' claimed invention, as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Five times amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a MMTV U3 sequence, [homologous to a PCR amplification product] wherein the MMTV U3 sequence is obtainable [by the] using a PCR amplification product that is amplified using primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a PCR template comprising a MMTV provirus [or a plasmid comprising a MMTV provirus as PCR template], and wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell.

11. (Twice amended) The retroviral vector according to claim 10, wherein said therapeutic gene is selected from the group consisting of: Herpes Simplex Virus thymidine kinase gene, cytosine deaminase gene, guanine phosphoribosyl transferase (gpt) gene, cytochrome P 450 gene, cell cycle regulatory genes, tumor suppressor genes, antiproliferation genes [or] and cytokines genes.

13. (Four times amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a MMTV U3 sequence, [homologous to a PCR amplification product] wherein the MMTV U3 sequence is obtainable [by the] using a PCR amplification product that is amplified using primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a PCR template comprising a MMTV provirus [or a plasmid comprising a MMTV provirus as PCR template], and wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell.

23. (Four times amended) A pharmaceutical composition comprising a DNA construct comprising a therapeutic gene placed under transcriptional control of a MMTV U3 sequence, [homologous to a PCR amplification product] wherein the MMTV U3 sequence is obtainable

[by the] using a PCR amplification product that is amplified using primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a PCR template comprising a MMTV provirus [or a plasmid comprising a MMTV provirus as PCR template], and wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell, and a pharmaceutically acceptable carrier or diluent.

26. (Five times amended) A method for the expression of a heterologous gene in a human cell comprising introducing a retroviral vector comprising said gene under transcriptional control of a MMTV U3 sequence, [homologous to a PCR amplification product] wherein the MMTV U3 sequence is obtainable [by the] using a PCR amplification product that is amplified using primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a PCR template comprising a MMTV provirus [or a plasmid comprising a MMTV provirus as PCR template], into the human cell and maintaining the cell under conditions in which the gene is expressed in the human cell.

32. (Twice amended) The method according to claim 31, wherein said therapeutic gene is selected from the group Herpes Simplex Virus thymidine kinase gene, cytosine deaminase gene, guanine phosphoribosyl transferase (gpt) gene, cytochrome P 450 gene, cell cycle regulatory genes, tumor supressor genes, antiproliferation genes [or] and cytokine genes.

53. (Twice amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a proximal 445 bp of the murine WAP [regulatory sequence] promoter which includes a transcription initiation site, wherein the WAP [regulatory sequence] promoter directs expression of the heterologous gene in a cell when the vector is introduced into the cell.

59. (Amended) The retroviral vector according to claim 58 wherein said therapeutic gene is selected from the group Herpes Simplex Virus thymidine kinase gene, cytosine deaminase gene, guanine phosphoribosyl transferase (gpt) gene, cytochrome P 450 gene, cell cycle regulatory genes, tumor supressor genes, antiproliferation genes [or] and cytokine genes.

61. (Amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a proximal 445 bp of the murine WAP [regulatory sequence] promoter which includes a transcription initiation site.

82. (Amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a [rodent] proximal 445 bp of the murine WAP [regulatory sequence] promoter which includes a transcription initiation site and wherein the WAP [regulatory sequence] promoter directs expression of the heterologous gene in a human mammary carcinoma cell when the vector is introduced into the cell.

87. (Amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a [rodent] proximal 445 bp of the murine WAP [regulatory sequence] promoter which includes a transcription initiation site.